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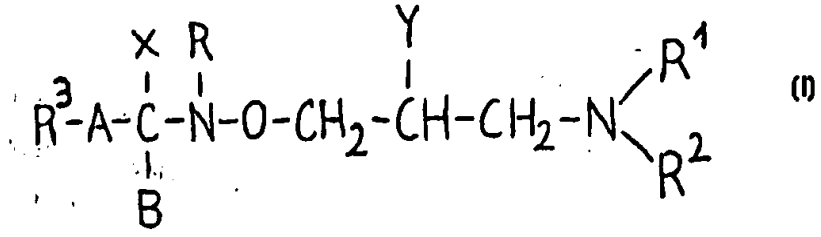

(I)

(57) Abstract

The invention refers to cosmetic compositions suitable for reducing the ageing processes of skin and/or treating the pathological lesions of skin, said compositions comprising a hydroximic acid derivative of formula (I).

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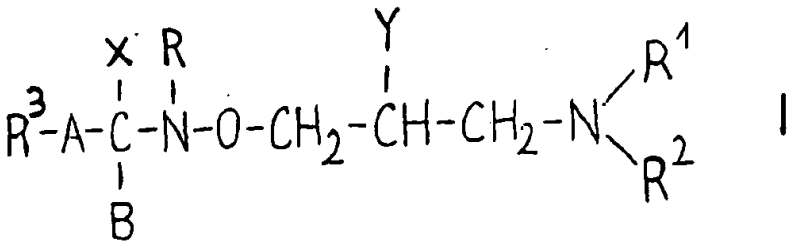
A cosmetic composition and a method for reducing the ageing processes of skin

The invention refers to a cosmetic composition and a method for reducing the ageing processes of skin and/or treating the pathological lesions of skin.

More specifically, the invention refers to a cosmetic composition comprising a hydroximic acid derivative of the formula



I

wherein

R^1 represents a hydrogen atom or a C_{1-5} alkyl group,

R^2 stands for a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group or a phenyl group optionally substituted by a hydroxy or a phenyl group, or

R^1 and R^2 together with the nitrogen atom they are attached to form a 5 to 8 membered ring optionally containing one or more further nitrogen, oxygen or sulfur atom(s) and said ring can be condensed with another alicyclic or heterocyclic ring, preferably

a benzene, naphthalene, quinoline, isoquinoline, pyridine or pyrazoline ring, furthermore, if desired and chemically possible, the nitrogen and/or sulfur heteroatom(s) are present in the form of an oxide or dioxide,

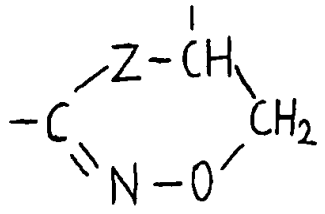
R^3 means a hydrogen atom, a phenyl group, a naphthyl group or a pyridyl group wherein said groups can be susbtituted by one or more halo atom(s) or C_{1-4} alkoxy group(s),

Y is a hydrogen atom, a hydroxy group, a C_{1-24} alkoxy group optionally substituted by an amino group, a C_{2-24} polyalkenyloxy group containing 1 to 6 double bond(s), a C_{1-25} alkanoyl group, a C_{3-9} alkenoyl group or a group of the formula R^7-COO- wherein R^7 represents a C_{2-30} polyalkenyl group containing 1 to 6 double bond(s),

X stands for a halo atom, an amino group, a C_{1-4} alkoxy group, or

X forms with B an oxygen atom, or

X and Y together with the carbon atoms they are attached to and the -NR-O-CH_2- group being between said carbon atoms form a ring of the formula



a

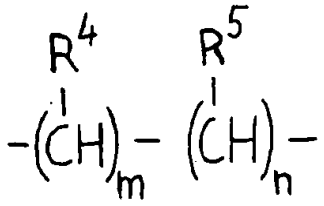
wherein

Z represents an oxygen atom or a nitrogen atom,

R stands for a hydrogen atom or

R forms with B a chemical bond,

A is a C_{1-4} alkylene group or a chemical bond or a group of the formula



b

wherein

R^4 represents a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group or a phenyl group optionally substituted by a halo atom, a C_{1-4} alkoxy group or a C_{1-5} alkyl group,

R^5 stands for a hydrogen atom, a C_{1-4} alkyl group or a phenyl group,

m has a value of 0, 1 or 2,

n has a value of 0, 1 or 2,

or a physiologically acceptable acid addition salt thereof as the active ingredient.

The human skin is a natural target of light radiation having several known pleasant and unpleasant effects such as sunburn and carcinogenesis. Due to the ultraviolet radiation, free radicals (for example hydroxy

radicals or nascent oxygen) form in the skin. Such free radicals can injure the DNA and contribute to the ageing of the skin.

A well-known theory of the ageing process of skin is based on the deteriorating effect of free radicals. In addition to the effect of ultraviolet radiation, free radicals may also form in biochemical processes. Thus, due to e.g. inflammation, hypoxia or reactive hyperaemia, free radicals of oxygen origin such as superoxide anion, perhydroxy or hydroxy radical, hydrogen peroxide etc. may form.

Free radicals having powerful oxidizing effect can injure the membrane by oxidizing the unsaturated fatty acid components of the membrane (peroxidization of lipids) on the one hand, and reactive aldehydes are formed during the oxidization on the other hand. In the injury of membrane, the increased intake of calcium leads to cell death, and pathological processes are started due to the presence of the reactive aldehydes:

- injury of DNA, mutation in both the cell nucleus and mitochondrium;
- change in the properties of the interstitial proteins (i.e. elastin) owing to formation of crosslinks.

It is known that the elastic structures of collagen proteins and elastin contain a lot of water. It is characteristic of the interstitial proteins that they are rich

in lysine. The reactive aldehydes such as malondialdehyde give condensation reaction with the side chains containing amino groups to yield crosslinks. Thus, the originally elastic structure becomes rigid and hydrophobic. During the above process, at first lipofuscin ceroids, then age pigments are formed.

The natural protective mechanisms against ultraviolet radiation include bronzing due to the formation of melanin, DNA repair mechanism etc. The deficiency of a protective mechanism such as the damage of the DNA repair and consequently the loss of the correction of the DNA injuries caused by the ultraviolet rays leads to the early ageing of skin or perhaps to a disease called xeroderma pigmentosum that can be accompanied by the development of a malignant tumor. Sunburn spots caused by bronzing in the early childhood are healed leaving an extended scar. In addition to spinocellular carcinoma, various malignant tumors (e.g. melanoma, cerato-acanthoma, basalioma, sarcoma) can develop.

Thus, it is of great significance if the ageing processes of skin could be influenced and the pathological lesions could be treated.

The hydroximic acid derivatives of the formula I are known. HU-P No. 177 578 and its equivalent US-P No. 4,308,399 describe

hydroximic acid derivatives within the compounds of the formula I suitable for the treatment of diabetic angiopathy.

HU-P No. 207 988 and its equivalent E-P No. 417 210 also describe hydroximic acid halides within the formula I having a selective beta-blocking effect, thus, being suitable for the treatment of diabetic angiopathy.

HU-P Application No. 2385/92 published under No. T/66350 describes further hydroximic acid derivatives within the formula I. These known compounds can be used in the treatment of vascular deformations, mainly in the therapy of diabetes mellitus.

The aim of the invention is to provide a composition suitable for reducing the ageing processes of skin and/or treating the pathological lesions of skin.

It was found that the above aim is fulfilled by a composition comprising a hydroximic acid derivative of the formula I or a physiologically acceptable acid addition salt thereof as the active ingredient.

Under the pathological lesions of skin for which the composition of the invention is suitable, especially the followings are meant:

- dry skin;
- actinic keratosis, aktinic prurigo (Lopez-Gonzalez's disease);

- polymorphic light exanthema;
- toxic photopathy;
- photo-allergy;
- purpura senilis;
- solar atrophy of skin;
- puberal strias (stria migrans);
- elastoma diffusum (old skin);
- X-ray dermatitis;
- gouty polychondritis;
- decubitus (bedsore).

In the description and Claims, under the term "composition" a cosmetic composition, or a medical cosmetic composition or a pharmaceutical composition is meant which is suitable, in the first place, for local treatment, and is applied to the skin surface in a conventional manner.

The composition of the invention comprises a hydroximic acid derivative of the formula I or a physiologically acceptable acid addition salt thereof as the active ingredient in admixture with one or more conventional carrier(s) of cosmetic compositions.

In the specification and Claims, a C_{1-5} alkyl group is, for example, a methyl, ethyl, n-propyl, isopropyl, n-butyl or n--pentyl group, preferably a methyl or an ethyl group.

A C_{3-8} cycloalkyl group is, for example, a cyclopropyl, cyclopentyl, cyclohexyl, cyclo-heptyl or cyclooctyl group, preferably a

cyclopentyl or a cyclohexyl group.

A 5 to 8 membered ring containing one or more heteroatom(s) can be, for example, a pyrrole, pyrazole, imidazole, oxazole, thiazole, pyridine, pyridazine, pyrimidine, piperazine, morpholine, indole, quinoline etc. ring.

A C_{1-24} alkoxy group is, for example, a methoxy, ethoxy, n-propoxy, tert.-butoxy, n-pentoxy, decyloxy, dodecyloxy, octadecyloxy etc. group.

A C_{1-25} alkanoyl group is, for example, a formyl, acetyl, propionyl, butiryl, caproyl, palmityl, stearyl etc. group.

A C_{3-9} alkenoyl group is, for example, an acryloyl, pentenoyl, hexenoyl, heptenoyl, octenoyl etc. group.

A C_{1-4} alkylene group is, for example, a methylene, ethylene, propylene or butylene group.

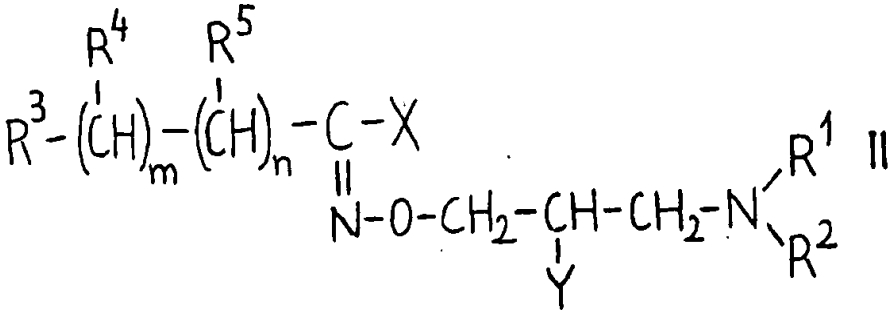
A halo atom is, for example, a fluoro, chloro, bromo or iodo atom, preferably a chloro or a bromo atom.

If Y stands for a group of the formula R^7-COO-, it can represent, for example, a linolenoyl, linoloyl, docosahexanoyl, eicosapentanoyl, arachidonoyl etc. group.

The physiologically acceptable acid addition salts of the compounds of the formula I are the acid addition salts formed with physiologically acceptable inorganic acids such as hydrochloric acid, sulfuric acid

etc. or with physiologically acceptable organic acids such as acetic acid, fumaric acid, lactic acid etc.

A preferred subgroup of the compounds of the formula I consists of the hydroximic acid derivatives of the formula

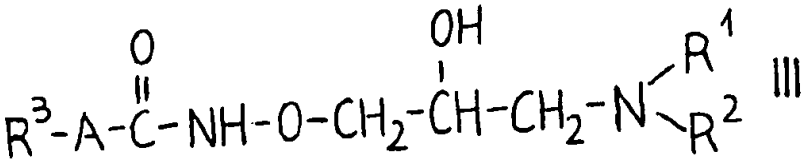


II

wherein R^1, R^2, R^3, R^4, R^5, m and n are as stated in relation to formula I, X represents a halo atom or an amino group, Y means a hydroxy group.

Especially preferred compounds of the formula II are those wherein R^1 and R^2 together with the nitrogen atom they are attached to form a piperidino group, R^3 stands for a pyridyl group, m and n have a value of 0, X is as defined above. Of these compounds, preferred species are as follows: O-(3-piperidino-2-hydroxy-1-propyl)pyrid--3-ylhydroximic acid chloride (Compound "A") and O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime (Compound "B").

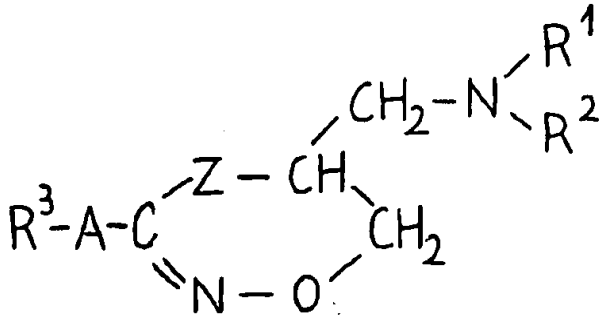
A further preferred subgroup of the hydroximic acid derivatives of the formula I consists of the compounds of the formula



III

wherein R^1, R^2, R^3 and A are as stated in relation to formula I.

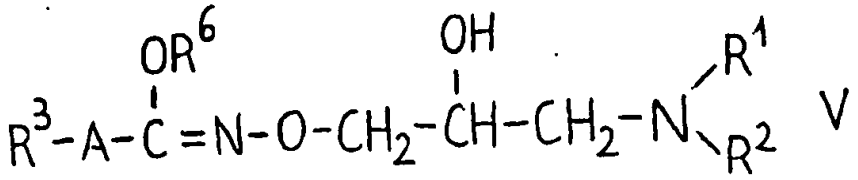
Another preferred subgroup of the hydroximic acid derivatives of the formula I consists of the compounds of the formula



IV

wherein R^1, R^2, R^3 and A are as stated in relation to formula I, Z represents an oxygen or a nitrogen atom.

A still further preferred subgroup of the hydroximic acid derivatives of the formula I consists of the compounds of the formula



wherein R^1, R^2, R^3 and A are as stated in relation to formula I, R^6 stands for a C_{1-4} alkyl group.

The compounds of the formula I can be prepared by the processes known from HU-P Nos. 177 578 and 207 988 as well as from HU-P Application published under No. T/66350.

The composition of the invention contains, in general, 0.1 to 30 % by mass, suitably 2 to 10 % by mass, preferably 4 to 5 % by mass of a hydroximic acid derivative of the formula I or a physiologically acceptable acid addition salt thereof as the active ingredient and conventional carrier(s) of the cosmetic compositions.

The compositions of the invention can be conventional cosmetic formulations suitable for the local treatment of the skin surface. Preferred formulations are creams, body emulsions, sun-emulsions, skin treatment foams, sprays, skin regenerating ampouls etc.

The compositions of the invention may contain, in addition to the active ingredient,

the conventional carriers of cosmetic compositions generally in an amount of 70 to 99.9 % by mass. Suitable carriers are, for example, one- or two-basic alcohols having a saturated or an unsaturated carbon chain such as cetyl alcohol, stearyl alcohol, cetyl-stearyl alcohol, oleyl alcohol, lauryl alcohol, ethylene glycol, propylene glycol, glycerol; natural fats and oils such as olive oil, avocado oil, wheat-germ oil, maize-germ oil, lanolin, cocoa-butter; higher hydro-carbons such as vaseline oil, vaseline; bee-wax; cellulose derivatives; emulgators such as sodium lauryl sulfate, fatty acid or oleic acid esters of sorbitan, fatty acid or oleic acid esters of poly(ethylene glycol)s, sorbitan ethers of fatty alcohols or oleic alcohols, poly(ethylene glycol) ethers of fatty alcohols or oleic alcohols, glycerides of fatty acids; vitamins, herb extracts such as camomile extract; preservatives such as methyl p-hydroxy- benzoate, chlorohexidine gluconate; light protecting factors etc.

The compositions of the invention are prepared by blending the ingredients thereof, in a manner known per se. In case of compositions based on a water/oil or oil/water emulsion, in general, the ingredients of the fatty phase and those of the aqueous phase are separately admixed, then the two phases are blended using a fatty phase of elevated temperature, if required. The active

ingredient of the formula I is added, preferably in an aqueous solution, to the fatty phase or to the mixture of the other ingredients.

The skin ageing inhibition effect of the compounds of the formula I was examined on guinea-pigs. The skin surface of 8 guinea-pigs was depilated, then, on both sides of the animals 1 cm^2 areas were irradiated by UV-B light of 100 mJ/cm^2 intensity. After the irradiation, one side of the animals was covered with the cream of Example 1 comprising 4 % by mass of compound "A" as the active ingredient. The other side of each animal was covered with a mixture of cosmetic carriers comprising no active ingredient (i.e. a cream corresponding to that of Example 1 was used, however, said cream contained water instead of the active ingredient, too). Thus, as a matter of fact, an internal control was used in the experiment.

In case of 4 animals, the treatment with the cream was performed immediately after the irradiation, then the treatment was repeated daily for a week (group I). In case of the other 4 animals, the skin surface irradiated was treated with the cream of the invention and the control cream, respectively, only 24 hours after the irradiation (group II).

In case of animals of group I, a minimal

erythema could be observed on the skin surface irradiated and treated with the composition of the invention 24 and 48 hours after the irradiation. On the skin surface used as the control, an area without epithelium could be noticed, and this state subsisted during the 7 days of observation. From the 4th day, no difference could be detected between the skin surface irradiated and treated with the composition of the invention and the surrounding skin area.

In case of animals of group II, on the treated area as well as on the control area, skin injuries (vesicula, bulla) could be observed, then an area without epithelium developped. On the 7th day after the irradiation, the area treated with the composition of the invention was epithelized.

On the basis of the above examination it can be established that the skin surface is protected from the damaging effects of the UV-B light by the composition of the invention and the compound of the formula I, respectively. If the skin surface is treated with the composition of the invention immediately after the irradiation, only a weak injury of the epithelium is experienced, at the most.

Skin injuries developped by UV-B radiation are healed owing to the treatment with the composition of the invention in a shorter time than without treatment. The

compound of the formula I exerts an epithelizing effect.

Thus, a further embodiment of the invention consists of a method for reducing the ageing processes of skin and/or treating the pathological lesions of skin, said method comprising treating the affected skin surface with a cosmetically effective non-toxic amount of a hydroximic acid derivative of the formula I or a physiologically acceptable acid addition salt thereof.

Suitably, the skin surface is treated with a cosmetic composition comprising 0.1 to 30 % by mass of a hydroximic acid derivative of the formula I or a physiologically acceptable acid addition salt thereof.

Preferably, the skin surface is treated with O-(3-piperidino-2-hydroxy-1-propyl)pyrid--3-ylhydroximic acid chloride or O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime or a physiologically acceptable acid addition salt thereof.

The invention is further elucidated by means of the following Examples.

Example 1

Cream (oil/water)

The cream consists of the following ingredients:

compound "A"	4.0 % by mass
cetylstearyl alcohol	7.5 % by mass
stearic acid	9.0 % by mass

glycerol monostearate	2.0 % by mass
sodium lauryl sulfate	0.5 % by mass
methyl p-hydroxybenzoate	0.1 % by mass
distilled water	76.9 % by mass
	100.0 % by mass

The lipophilic ingredients (cetylstearyl alcohol, stearic acid and glycerol monostearate) are melted on a water-bath. The sodium lauryl sulfate and methyl p-hydroxybenzoate are dissolved in about 38 ml of distilled water at 60 to 65 ^{o}C, the pH of the solution is adjusted by the addition of diluted aqueous sodium hydroxide solution to a value of 9 to 10, then the aqueous solution is admixed to the mixture of the lipophilic ingredients, and the emulsion obtained is stirred until cold. The active ingredient is dissolved in the remaining water and the solution is admixed to the cooled cream.

Example 2

Cream (water/oil)

The cream consists of the following ingredients:

compound "A"	5.0 % by mass
cetylstearyl alcohol	10.0 % by mass
white wax	10.0 % by mass
neutral oil	35.0 % by mass
Imwitor$^{(R)}$ 780 K (partial glycerides of vegetable fatty acids)	5.0 % by mass

methyl p-hydroxybenzoate	0.1 % by mass
distilled water	34.9 % by mass
	100.0 % by mass

The ingredients are blended using the method described in Example 1.

Example 3

Cream (water/oil)

The cream consists of the following ingredients:

compound "A"	5.0 % by mass
cetylstearyl alcohol	1.5 % by mass
white wax	1.5 % by mass
lanalcol	2.5 % by mass
cholesterol	1.0 % by mass
white vaseline	43.5 % by mass
sodium tetraborate	2.0 % by mass
methyl p-hydroxybenzoate	0.1 % by mass
distilled water	42.9 % by mass
	100.0 % by mass

The ingredients are blended using the method described in Example 1.

Example 4

Moisturizing cream for night

The cream consisting of the following ingredients is prepared using the method described in Example 1:

compound "B"	5.0 % by mass
cetyl alcohol	5.0 % by mass
lanolin (anhydrous)	5.0 % by mass
cocoa-butter	5.0 % by mass

vaseline	5.0 % by mass
vaseline oil	5.0 % by mass
isopropyl miristate	1.0 % by mass
isopropyl palmitate	1.0 % by mass
wheat-germ oil	10.0 % by mass
evening primrose oil	5.0 % by mass
vitamin A	0.03% by mass
vitamin E	0.05% by mass
glycerol	5.0 % by mass
propylene glycol	5.0 % by mass
methyl p-hydroxybenzoate	0.2 % by mass
perfume	0.1 % by mass
water, demineralized	42.62% by mass
	100.00% by mass

Example 5

Moisturizing cream for day

The cream consisting of the following ingredients is prepared by the method described in Example 1.

compound "B"	5.0 % by mass
cetyl alcohol	5.0 % by mass
lanolin (anhydrous)	5.0 % by mass
vaseline	5.0 % by mass
vaseline oil	5.0 % by mass
isopropyl miristate	1.0 % by mass
isopropyl palmitate	1.0 % by mass
borage oil	4.0 % by mass
peanut oil	11.0 % by mass
vitamin A	0.03% by mass
vitamin E	0.05% by mass
glycerol	5.0 % by mass

propylene glycol	5.0 % by mass
methyl p-hydroxybenzoate	0.2 % by mass
perfume	0.1 % by mass
water, demineralized	47.62 % by mass
	100.00% by mass

Example 6

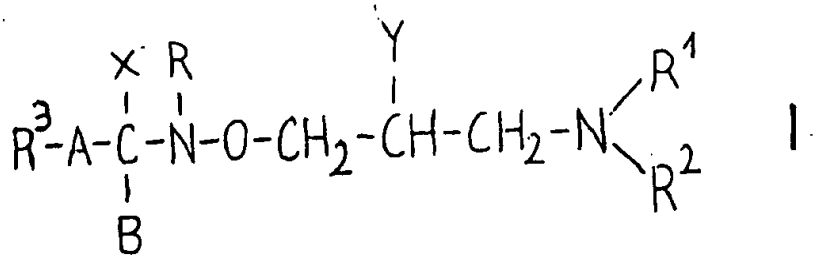
Body milk

The body milk consisting of the following ingredients is prepared by the method described in Example 1.

compound "B"	4.0 % by mass
stearic acid monoglyceride	2.0 % by mass
cetylstearyl alcohol	2.0 % by mass
peanut oil	5.0 % by mass
vaseline oil	3.0 % by mass
polyoxyethylene cetylstearyl alcohol (degree of polymerization: 20)	2.0 % by mass
glycerol	4.0 % by mass
methyl p-hydroxybenzoate	0.2 % by mass
propyl p-hydroxybenzoate	0.1 % by mass
butylhydroxytoluene	0.01% by mass
water, demineralized	77.69% by mass
	100.00% by mass

Claims

1. A cosmetic composition comprising a hydroximic acid derivative of the formula



I

wherein

R^1 represents a hydrogen atom or a C_{1-5} alkyl group,

R^2 stands for a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group or a phenyl group optionally substituted by a hydroxy or a phenyl group, or

R^1 and R^2 together with the nitrogen atom they are attached to form a 5 to 8 membered ring optionally containing one or more further nitrogen, oxygen or sulfur atom(s) and said ring can be condensed with another alicyclic or heterocyclic ring, preferably a benzene, naphthalene, quinoline, isoquinoline, pyridine or pyrazoline ring, furthermore, if desired and chemically possible, the nitrogen and/or sulfur heteroatom(s) are present in the form of an oxide or dioxide,

R^3 means a hydrogen atom, a phenyl group,

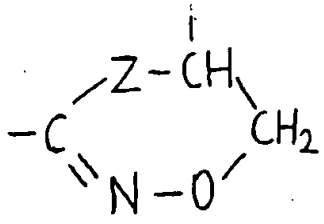
a naphthyl group or a pyridyl group wherein said groups can be substituted by one or more halo atom(s) or C_{1-4} alkoxy group(s),

Y is a hydrogen atom, a hydroxy group, a C_{1-24} alkoxy group optionally substituted by an amino group, a C_{2-24} polyalkenyloxy group containing 1 to 6 double bond(s), a C_{1-25} alkanoyl group, a C_{3-9} alkenoyl group or a group of the formula R^7-COO- wherein R^7 represents a C_{2-30} polyalkenyl group containing 1 to 6 double bond(s),

X stands for a halo atom, an amino group, a C_{1-4} alkoxy group, or

X forms with B an oxygen atom, or

X and Y together with the carbon atoms they are attached to and the -NR-O-CH_2- group being between said carbon atoms form a ring of the formula



a

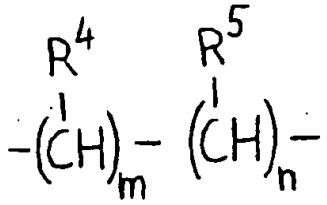
wherein

Z represents an oxygen atom or a nitrogen atom,

R stands for a hydrogen atom or

R forms with B a chemical bond,

A is a C_{1-4} alkylene group or a chemical bond or a group of the formula



b

wherein

R^4 represents a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group or a phenyl group optionally substituted by a halo atom, a C_{1-4} alkoxy group or a C_{1-5} alkyl group,

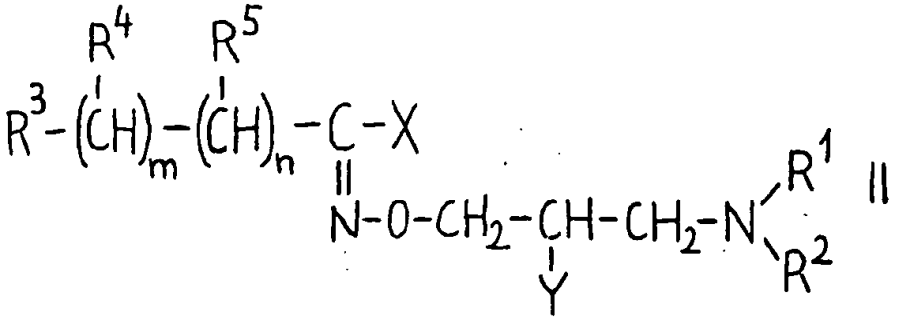
R^5 stands for a hydrogen atom, a C_{1-4} alkyl group or a phenyl group,

m has a value of 0, 1 or 2,

n has a value of 0, 1 or 2,

or a physiologically acceptable acid addition salt thereof as the active ingredient in admixture with one or more conventional carrier(s).

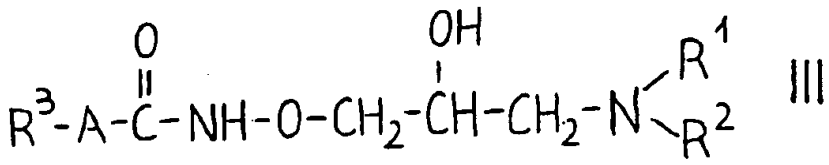
2. A cosmetic composition of Claim 1 in which the active ingredient is a compound of the formula



II

wherein R^1, R^2, R^3, R^4, R^5, m and n are as stated in Claim 1, X represents a halo atom or an amino group, Y stands for a hydroxy group, or a physiologically acceptable acid addition salt thereof.

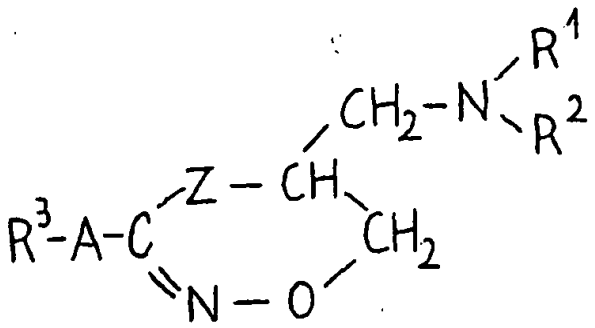
3. A cosmetic composition of Claim 1 in which the active ingredient is a compound of the formula



III

wherein R^1, R^2, R^3 and A are as defined in Claim 1, or a physiologically acceptable acid addition salt thereof.

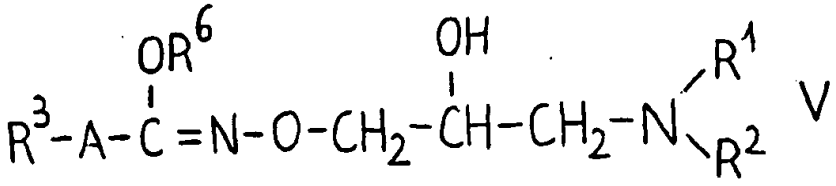
4. A cosmetic composition of Claim 1 in which the active ingredient is a compound of the formula



IV

wherein R^1, R^2, R^3 and A are as stated in Claim 1, Z represents an oxygen or a nitrogen atom, or a physiologically acceptable acid addition salt thereof.

5. A cosmetic composition of Claim 1 in which the active ingredient is a compound of the formula



V

wherein R^1, R^2, R^3 and A are as defined in Claim 1, R^6 represents a C_{1-4} alkyl group, or a physiologically acceptable acid addition salt thereof.

6. A cosmetic composition of Claim 1 or 2 in which the active ingredient is a compound of the formula II, wherein R^1 and R^2 together with the nitrogen atom they are attached to form a piperidino group, m and

n have the value of 0, X and Y are as stated in Claim 2, or a physiologically acceptable acid addition salt thereof.

7. A cosmetic composition of Claim 1, 2 or 6 in which the active ingredient is O-(3-piperidino-2-hydroxy-1-propyl)pyrid-3-ylhydroximic acid chloride or a physiologically acceptable acid addition salt thereof.

8. A cosmetic composition of Claim 1, 2 or 6 in which the active ingredient is O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime or a physiologically acceptable acid addition salt thereof.

9. A cosmetic composition of any of Claims 1 to 8 comprising 0.1 to 30 % by mass of the active ingredient.

10. A method for reducing the ageing processes of skin and/or treating the pathological lesions of skin in which the affected skin surface is treated with a cosmetically effective non-toxic amount of a hydroximic acid derivative of the formula I, wherein R, R^1, R^2, R^3, X, Y and B are as defined in Claim 1, or a physiologically acceptable acid addition salt thereof.

11. A method of Claim 10 in which the skin surface is treated with a cosmetic composition comprising 0.1 to 30 % by mass of a hydroximic acid derivative of the formula I, wherein R, R^1, R^2, R^3, X, Y and B are as defined in Claim 1, or a physiologically

acceptable acid addition salt thereof.

12. A method of Claim 10 or 11 in which the hydroximic acid derivative is O-(3-piperidino-2-hydroxy-1-propyl)pyrid-3-ylhydroximic acid chloride.

13. A method of Claim 10 or 11 in which the hydroximic acid derivative is O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/HU 96/00081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 04584 A (BIOREX KUTATO FEJLESZTO) 3 May 1990 cited in the application see claims 1,7 ---	1,7,8
A	FR 1 404 481 A (F. HOFFMANN-LA ROCHE) 10 November 1965 see page 2, line 33 - line 45; claim 1 ---	1,7,8
A	GB 2 049 419 A (FERROKEMIA IPARI SZÖVETKEZET) 31 December 1980 see claim 1 ---	1,7,8
A	EP 0 583 479 A (OTSUKA PHARMACEUTICAL) 23 February 1994 see claims 21,30 ---	1,7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 1997	24.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ..al Application No
PCT/HU 96/00081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 362 845 A (CHINOIN GYOGYSZER ES VEGYESZETI TERMEREK GYARA) 24 March 1978 see claims 1,7 -----	1,7,8

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 96/00081

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6, 9-11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

PLEASE SEE CONTINUATION SHEET

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/HU 96/ 00081

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

As the drafting of the claims is not clear and concise (Art.6, PCT) and encompasses such an enormous amount of products, a complete search is not possible on economic grounds (See art. 17 (2) (a) (ii), PCT). Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been based on the examples.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/HU 96/00081

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